amended to specify that the fibrinogen is "from a sample of non-human mammalian blood plasma with polyethylene glycol such that at least about 90% of the fibrinogen present in the sample is recovered." It is submitted that the words "high yield" in the claims clearly refer to the claim language reciting "at least about 90% of the fibrinogen present in said sample is recovered," and thus the claims are definite in scope. Similarly, Claims 36 and 37 require precipitating fibrinogen from a sample of "non-human" mammalian blood plasma with polyethylene glycol 1000.

Additionally, Claims 2, 13 and 37 indicate that the fibrinogen has a concentration of about 30 mg/ml or less at the site of treatment. Similarly, Claims 1 and 36 specify that the fibrinogen has a concentration of about 10 mg/ml or less at the site of treatment.

Support for the above claims exists throughout the specification, for example, at page 5, lines 3-8, page 7, lines 20-22 and page 10, lines 18-19.

In the interest of advancing the prosecution of the subject application, Applicants herein address each of the Examiner's rejections set forth in the Final Official Action for parent application Serial No. 08/805,703, now abandoned in view of the filing of the subject continuation application. Specifically, in the Final Official Action, Claims 1-2, 5-6, 8-9, 13 and 49-51 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,377,572 to Schwarz et al. ("Schwarz"). Applicants respectfully assert that the present claims and remarks obviate these rejections.

Independent Claims 1, 2, 13, 36 and 37 of the subject application are directed to particular therapeutic compositions having a high yield of fibrinogen. Significantly, the fibrinogen is obtained from a sample of non-human mammalian blood plasma with polyethylene glycol such that at least about 90% of the fibrinogen present in the sample is recovered. Additionally, Claims 2, 13 and 37 require fibrinogen to be made present at the

site of treatment at a concentration of about 30 mg/ml or less, and Claims 1 and 36 require fibrinogen at a concentration of about 10 mg/ml or less at the site of treatment. Applicants' Claims 5-6, 8-9 and 35 each depend either directly or indirectly from Claim 1 or 2 and specify further advantageous features of the present invention.

Referring now to the Schwarz reference cited by the Examiner, it is respectfully asserted that this reference does not disclose nor suggest Applicants' presently claimed invention. For example, the tissue adhesive of Schwarz includes fibrinogen in an amount of at least 70 mg/ml (Col. 1, lines 57-61). Moreover, Schwarz is also cited and distinguished in Applicants' specification at page 4, line 21 continuing to page 5, line 19. As described therein:

> [t]herapeutic adhesive fibrinogen compositions disclosed therein are stated to require concentrations of fibrinogen of at least about 70 mg/ml (which may again be diluted 1:1 at the treatment site by contact with a thrombin-containing solution).
>
> The present invention relates to fibrinogen-containing compositions that have surprising clinical (medical) utility as adhesives, sealants, or hemostatic agents, and that provide therapeutically effective strength at fibrinogen concentrations at the treatment site of, for example, only about 10 mg/ml. The more dilute and less viscous nature of the therapeutic compositions provided according to the practice of the present invention decreases substantially the time necessary to resuspend such compositions from the lyophilized form, an important advantage in, for example, the hospital emergency room. Filtration of the fibrinogen during processing is also facilitated. In preferred form the fibrinogen used in the therapeutic compositions of the invention is of nonhuman mammalian origin, eliminating risk of contamination of product with human viruses.

Thus, the tissue adhesive of Schwarz, including at least about 70 mg/ml of fibrinogen, appears to even teach away from the present invention. Accordingly, the Examiner's rejection is believed to be overcome.

In the afore-referenced Final Official Action, Claims 1-3, 7-11, 13-14 and 49-51 were then rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,427,650 to Stroetmann ("Stroetmann '650") or U.S. Patent No. 4,442,655 to Stroetmann ("Stroetmann '655"). Similarly, Claims 1-3, 5-11, 13-14 and 49-51 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Stroetmann '650 or Stroetmann '655 in view of the article, entitled, *The Measurement of Fibrino gen and its Derivatives* by Farrell et al. ("Farrell").

Independent Claims 1, 13, 36 and 37 have been described above in detail. Claims 2-3, 5-11, 14 and 35 each depend either directly or indirectly from independent Claim 1 or 2 and recite further advantageous features of the present invention.

In contrast to the present invention, Stroetmann '650 is directed to enriched plasma derivative for advancement of wound closure and healing, wherein the fibrinogen is isolated from *human plasma* (Col. 3, line 17, emphasis added). Specifically, Stroetmann '650 discloses that "it has been recognized according to the invention that the fibrinogen isolated from human plasma shall largely be free from cryo-insoluble globulin. The presence of cryo-insoluble globulin impairs the fibrin formation and impedes the healing of the wound . . . Such a fibrinogen largely liberated from cryo-insoluble globulin may be obtained from human plasma by precipitation with a mixed solvent containing glycine, β-alanine and ethanol and subsequent dialysis and lyophilization of the precipitate" (Col. 3, lines 15-31).

However, in the presently claimed invention, the fibrinogen is advantageously obtained from non-human mammals. As described in Applicants' specification at page 10, line 15 continuing to page 12, line 10:

> [t]he therapeutic compositions of the invention comprise non-autologous, non-single donor mammalian fibrinogen, that is, they comprise fibrinogen derived (pooled) from multiple mammalian donors. Preferred donors are mammals other than the human . . . Fibrinogen-based adhesives (fibrin

> glues) are accepted for therapeutic use in Europe. It is noted however that such compositions, if made from pooled human donor plasma, are not approved for therapeutic use in the United States because of the risk of transmission of viral disease such as AIDS and hepatitis B and C. Numerous incidents of infection have been reported . . . An alternate resolution to the above-mentioned risk of viral infection, characteristic of human plasma-derived therapeutic products, is to provide fibrinogen from a mammalian source other than from humans. Fibrinogen compositions that could be provided from mammalian species other than the human are disclosed, for example, in U.S. Patents No. 4,377,572 and 4,362,567. However, the therapeutic compositions defined therein are stated to contain at least about 70 mg/ml or more of fibrinogen (prior to any dilution at the site of treatment) leading potentially to the presence also therein of a substantial amount of additional and antigenic protein impurities, there resulting an associated risk of severe immune response. . .

Thus, Stroetmann '650 also appears to teach away from the presently claimed invention, as is the case for Stroetmann '655. That is, Stroetmann '655 discloses that "[p]referably, a relatively high fibrinogen concentration of approx. 50-80 mg/ml is provided . . . Therefore, an increased fibrinogen concentration in the initial solution leads to a denser end product of higher mechanical strength" (Col. 4, lines 14-21).

Moreover, the addition of Farrell does not cure the shortcomings of either Stroetmann '650 or '655. For example, Farrell is a technical paper merely documenting the investigation of the minimal concentration of ε-amino caproic acid in plasma required to induce total suppression of *in vitro* fibrinogenolysis and fibrinolysis, as well as the effect this EACA concentration produced on recovery of thrombin clottable fibrinogen estimates. These results were compared with clot recovery from plasma to which either fibrin degradation products or fibrinogen degradation products had been added (*See*, page 328 of Farrell).

For the foregoing reasons, it is respectfully asserted that there is no teaching, suggestion or motivation in either Stroetmann '650 or Stroetmann '655 which would lead one of ordinary skill in the art to modify either of these references in an attempt to arrive at

the presently claimed invention. Nor is there any suggestion in either Stroetmann '650, Stroetmann '655 or Farrell which would lead one of ordinary skill in the art to combine and modify these references, and the Examiner has pointed to no such suggestion. For example, both Stroetmann '650 and '655 teach away from the present invention, and the addition of Farrell does not cure the shortcomings of either reference. Accordingly, in view of the foregoing amendments and remarks, the Examiner's rejection is believed to be met and should be withdrawn.

Claims 1-4, 7-11, 13-14 and 49-51 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Stroetmann '650 or Stroetmann '655 in view of U.S. Patent No. 5,116,950 to Miyano et al. ("Miyano").

The teachings of Stroetmann '650 and Stroetmann '655 have been described above in detail, and it is respectfully asserted that the addition of Miyano to either of these references neither discloses nor suggests Applicants' presently claimed invention. That is, Miyano relates to a process for heat treating an aqueous solution containing fibrinogen to thereby inactivate virus(es) therein (Col. 1, lines 5-8). According to Miyano, fibrinogen is frequently accompanied by a risk of contamination with virus(es), in particular, hepatitis or AIDS virus. Thus, it should be heated to inactivate these viruses. However, fibrinogen is unstable to heat and thus inactivated during the conventional liquid heating process. Accordingly, it has been desired to provide a process for heating fibrinogen to inactivate viruses contaminating the same without inactivating the fibrinogen per se (Col. 1, lines 28-36).

Thus, Miyano even addresses a problem distinct from that which is addressed and solved by the present invention and one skilled in the art would not even be motivate to look to Miyano for guidance, let alone combine this reference with either Stroetmann '650

or Stroetmann '655 for the foregoing reasons. Withdrawal of this rejection is therefore believed to be warranted.

Claims 2, 12 and 49-51 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Stroetmann '655 in view of the abstract of *Preparation of Rat Fibrinogen* by Richter et al. ("Richter").

The advantageous features of Claim 2 and Claims 35-37 (corresponding, in part, to Claims 49-51 of the parent application) have been previously described. Claim 12 depends from amended Claim 2 and is directed to a fibrinogen-containing therapeutic composition comprising, as percent by weight of total protein contained therein, clottable fibrinogen, at about 56% or greater; serum albumin, at less than about 20%; plasminogen, at less than about 1%; and plasma fibronectin, at less than about 3%.

It is respectfully asserted that the addition of Richter to Stroetmann '655 neither discloses nor suggests Applicants' presently claimed invention. That is, Richter is directed to the preparation of rat fibrinogen and a comparison of the intermediate, as well as final products, of rat fibrinogen with those of human fibrinogen (Abstract). Stroetmann '655 teaches that "[p]referably, a relatively high fibrinogen concentration of approx. 50-80 mg/ml is provided . . . Therefore, an increased fibrinogen concentration in the initial solution leads to a denser end product of higher mechanical strength" (Col. 4, lines 14-21).

In contrast, amended Claim 2, from which Claim 12 depends, and Claim 37 require fibrinogen at the site of treatment at a concentration of about 30 mg/ml or less. Similarly, Claim 35 depends from Claim 1 which requires fibrinogen at the site of treatment at a concentration of about 10 mg/ml or less, as also required by Claim 36.

It is respectfully asserted that there is no teaching or suggestion in either Stroetmann '655 or Richter which would motivate one of ordinary skill in the art to combine and modify these references in an attempt to arrive at the presently claimed invention, and the Examiner has pointed to no such suggestion. In view of the foregoing, withdrawal of this rejection is also believed to be warranted.

For the foregoing reasons, Applicants' presently claimed invention provides a very useful and therapeutic composition which is neither anticipated nor rendered obvious by the afore-cited references, whether the references are viewed alone or in combination. Moreover, none of the afore-cited references whether viewed alone or in combination, discloses or suggests Applicants' therapeutic composition having a high yield of fibrinogen, wherein the composition comprises non-autologous, non-single donor mammalian fibrinogen from a sample of non-human, mammalian blood plasma with polyethylene glycol such that at least about 90% of the fibrinogen present in the sample is recovered.

Turning now to the Examiner's particular comments set forth in the Final Official Action, the Examiner alleges that it would have been obvious to optimize the concentration used since the references encompass rations of fibrinogen, globulin and albumin (See Action, page 3, paragraph 4 and page 4, paragraph 8). The Examiner further contends that "[a]s for the concentration, generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. 'Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.' In re Abler . . ." (*See* Office Action dated April 13, 1998).

For the reasons set forth above in detail, it is respectfully asserted that "the general conditions" of the present claims are not disclosed in, nor suggested by, the afore-cited

references. Moreover, the significance of Applicants' claimed invention, particularly the concentration, has been established. For instance, as indicated in Applicants' specification at page 5, lines 3-15:

> [t]he present invention relates to fibrinogen-containing compositions that have surprising clinical (medical) utility as adhesives, sealants, or hemostatic agents, and that provide therapeutically effective strength at fibrinogen concentrations at the treatment site of, for example, only about 10 mg/ml. The more dilute and less viscous nature of the therapeutic compositions provided according to the practice of the present invention decreases substantially the time necessary to resuspend such compositions from the lyophilized form, an important advantage in, for example, the hospital emergency room. Filtration of the fibrinogen during processing is also facilitated.

Additionally, as indicated at page 9, lines 16-27 and page 14, lines 9-20 of Applicants' specification:

> the novel compositions of the present invention have important clinical benefits. In particular, since only a low concentration of fibrinogen is contained therein, and said fibrinogen is of a soluble and clottable character, the compositions can be resuspended from the lyophilized state for clinical use very rapidly, thereby facilitating emergency treatments and/or minimizing the time needed to complete surgical procedures. Filtration of fibrinogen solutions during processing (such as through a 0.22 micron filter) is also facilitated thereby. . . The use of numerous fibrinogen-containing compositions known in the art has been stated to require the presence therein of a minimum of about 70 mg/ml of fibrinogen, there being derived therefrom, fibrinogen, of at least about 35 mg/ml, at the treatment site. The fibrinogen-containing therapeutic compositions of the present invention are effective, however, even when the final concentration of fibrinogen derived therefrom at the treatment site (taking into account the volume of any thrombin solution applied therewith) is only about 10 mg/ml or lower.

All issues raised by the Examiner in parent application Serial No. 08/805,703 having been addressed, it is respectfully submitted that the subject application is in condition for allowance.

The Examiner is invited to telephone the undersigned attorney at 212-425-7200 with any questions or comments regarding this Amendment.

Authorization is also hereby given to charge any deficiency in fees in connection with this Amendment to our Deposit Account No. 11-0600.

Respectfully submitted,

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